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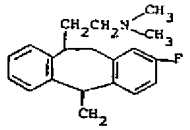
(72) Inventors WILLIAM JOSEPH HOULIHAN and JEFFREY NADELSON

(54) 10-(2-DIMETHYLAMINOETHYL)-10,11-DIHYDRO-2-FLUORO-5-METHYLENE-5H-DIBENZO[a,d]CYCLOHEPTENE

(71) We, SANDOZ -LTD., of Lichtstrasse 35, CH-4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to a noved dibenzocycloheptene derivative.

More particularly, the invention provides 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene of formula I,



I

The compound of formula I possesses pharmacological activity. In particular, it possesses antidepressant activity as indicated, e.g. by its activity in mice administered the compound intraperitoneally and tested according to the method basically as described by Spencer P. S. J., Antagonism of Hypothermia in the Mouse by Antidepressant Drugs, pp. 194—204, Ed. S. Garattini and M. N. G. Dukes, Excerpta Medica Foundation, 1967, and by its activity in cats tested for the compound's effect on 5 - hydroxytryptophan and l - tryptophan induced spinal monosynaptic reflex transmission, basically as described by Anderson, E. G. and Shibuya, T. The Effects of 5 - Hydroxytryptophan and l - Tryptophan on Spinal Synoptic Activity, pp. 352—360, J. Pharm. Exp. Therap. *153* (2) 1966). The compound is accordingly indicated for use as an antidepressant. An indicated suitable daily dosage is from 30 to 750 mg, conveniently administered in divided doses of from 7.5 to 375 mg, two to four times daily, or in retard form.

For the above mentioned use, the compound may be administered in free base or in the form of a pharmaceutically acceptable acid addition salt, which salt forms possess the same order of activity as the free base form. Suitable acids for salt formation include mineral acids, such as hydrochloric, sulphuric and phosphoric acids, and organic acids, such as succinic, benzenesulphonic and maleic acids.

The compound may be admixed with conventional pharmaceutically acceptable diluents or carriers, and, optionally, other excipients, and administered in such forms as capsules.

The compound of formula I falls within the class of compounds disclosed and claimed in our British Patent No. 1,419,681, and may be produced by the methods described therein. The present compound has been found to have particularly pronounced activity.

The following Examples 3 to 5 illustrate the production of the compound of formula I.

EXAMPLE 1:

4 - Fluoro - 2 - β - [2 - dimethylaminoethyl] - β - hydroxyphenethyl) - N - methylbenzamide

To a flask equipped with a stirrer, dropping funnel, condenser and gas inlet tube maintained under a nitrogen atmosphere there is added at room temperature 46.8 g. (0.28 mole) of *o* - methyl - N - methyl - *p* - fluoro - benzamide and 250 ml. of anhydrous tetrahydrofuran. The reaction flask is immersed in an ice bath and cooled to an internal temperature of 5°C. Stirring is initi-

ated and 360 ml. of 1.6 m. n - butyllithium (0.616 mole) in hexane is added dropwise for about 1 hour maintaining the temperature below 8°C. The resulting red dilithio salt is stirred at 5°C. for one additional hour and the reaction flask is then immersed in a dry-ice acetone bath and cooled to an internal temperature of —30° C. To the cold reaction mixture a solution of 49.7 g. (0.28 mole) 3 - dimethylaminopropiophenone in 140 ml. anhydrous tetrahydrofuran is added dropwise in *ca.* 45 minutes maintaining the temperabetween —30°C. and —20°C. The resulting reaction mixture is stirred at —25°C. for 1 hour, allowed to warm to —10°C. in *ca.* 1 hour, and then treated with 200 ml. of saturated aqueous ammonium chloride while maintaining the temperature below 0°C. The resulting solid is filtered, washed thoroughly with water and recrystallized from methylene chloride-ether (1:1) to give 4 - fluoro - 2 - (β - [2 - dimethylaminoethyl] - β - hydroxyphenethyl) - N - methylbenzamide.

EXAMPLE 2:

6 - Fluoro - 3 - [2 - dimethylaminoethyl] - 3,4 - dihydro - (3 - phenyl) - isocoumarin

To a flask equipped with a stirrer, condenser and gas inlet tube maintained under a nitrogen atmosphere there is added at room temperature 17.2 g (0.05 mole) of 4 - fluoro - [β - [2 - dimethylaminoethyl] - β - hydroxyphenethyl) - N - methyl - benzamide and 170 ml of o - dichloro benzene. Stirring is initiated and the mixture is heated at reflux for 18 hours. The excess *o* - dichlorobenzene is then removed by distillation *in vacuo* and the resulting oil is crystallized from ether to give 6 - fluoro - 3 - [2 - dimethylaminoethyl] - 3,4 - dihydro - (3 - phenyl) - isocoumarin.

EXAMPLE 3:

10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 7 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene

a) 4 - fluoro - 2 - (β - [2 - dimethylaminoethyl)phenethyl)benzoic acid hydrochloride

A solution of 15.65 g (0.05 mole) of 6 - fluoro - 3 - (2 - dimethylaminoethyl) - 3,4 - dihydro - 3 - phenylisocoumarin in 150 ml ethanol containing 1 g. 10% palladium on charcoal is hydrogenated at 50 psi and room temperature until one equivalent of hydrogen is absorbed. After addition of one equivalent of hydrochloric acid, the mixture is filtered and evaporated to give the intermediate 4 - fluoro - 2 - [2 - dimethylaminoethyl] - phenethyl)benzoic acid hydrochloride.

b) 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5H - dibenzo[a,d] - cyclohepten - 5 - one hydrochloride

A mixture of 15.65 g. (0.05 mole of 4 - fluoro - 2 - (β - dimethylaminoethyl]phenethyl)benzoic acid hydrochloride and 150 g of polyphosphoric acid is heated at 110°C for 6 hours allowed to cool and poured onto crushed ice with stirring. The resulting solution is cooled on ice and made basic by the addition of solid potassium hydroxide, and extracted with methylene chloride. The methylene chloride is wished with water, dried over anhydride magnesium sulfate and evaporated *in vacuo*. The residue is dissolved in isopropanol, and treated with gaseous hydrogen chloride. The resulting precipitate is filtered and recrystallized from isopropanol to give the intermediate 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5H - dibenzo[a,d]cyclohepten - 5 - one hydrochloride, which may be converted to the free base form by treatment with one equivalent of sodium hydroxide.

Following the above procedure and using an equivalent amount of ferric chloride in place of polyphosphoric acid, there is obtained the identical product.

Similarly using ferric chloride and 4 - fluoro - 2 - (β - dimethylaminoethyl] - phenethyl)benzoic acid chloride in place of 4 - fluoro - 2 - (β - [2 - dimethylaminoethyl] - phenethyl)benzoic acid hydrochloride, the identical product is again obtained.

Following the above detailed procedure but using 17.8 g. of 4 - fluoro - (p - [2 - dimethylaminoethyl] - phenethyl)benzoic acid ethyl ester in place of 14.75 g of 4 - fluoro - 2 - (β - [2 - dimethylaminoethyl) - phenethyl)benzoic acid hydrochloride, there is again obtained the identical product.

c) 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 5 - methyl - 2 - fluoro - 5H - dibenzo[a,d]cyclohepten - 5 - ol

To a solution of 20.7 g. (0.07 mole) of 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5H - dibenzo[a,d]cyclohepten - 5 - one in 200 ml. diethylether, under nitrogen, cooled to —5°C. 70 ml. 1.5N methyllithium (0.105 mole) in diethylether is added dropwise with stirring, maintaining temperature below 0°C., 15 minutes after the addition is complete the reaction is quenched by the addition of 50 ml. saturated ammonium cholride solution. The organic layer is separated, extracted with saturated sodium chloride solution, dried over anhydrous magnesium sulfate and evaporated. The crystalline residue is recrystallized from methylene-chloride - methanol 1:1 to give the intermediate 10 (2 - dimethylaminoethyl) - 10,11 - dihydro - 5 - methyl - 2 - fluoro - 5H - dibenzo[a,d]cyclohepten - 5 - ol.

Following the above procedure and using an equivalent amount of methylmagnesium chloride in place of methyllithium at room temperature instead of 0°C. for 3 hours in-

stead of 15 minutes, the identical product is again obtained.

d) 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene

A mixture of 8.5 g (0.027 mole) of 10 - 2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methyl - 5H - dibenzo[a,d]-cyclohepten - 5 - ol and 250 ml 2M - sulfuric acid is refluxed for 2 hours. The mixture is cooled in ice and made basic by the addition of solid potassium hydroxide. The mixture is extracted with methylene chloride. The methylene chloride is washed with water, dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The oily residue is distilled at 140°C/0.5 mm and the distillate is dissolved in ethanol and treated with maleic acid. The precipitate is filtered and recrystallized from diethylether - ethanol 1:1 to give the product 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene, in maleate salt form, m.p. 140°—142°C.

Following the above procedure and using an equivalent amount of ferric chloride in place of sulfuric acid, there is obtained the identical product.

EXAMPLE 4:

10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene

A mixture of 2.3 g (0.1 mole) of sodium hydride and 50 ml dimethylsulfoxide are heated at 75—80°C until hydrogen evolution has ceased. The mixture is cooled in an ice-bath and 35.7 (0.1 mole) of methyl triphenyl phosphonium bromide in 100 ml dimethyl sulfoxide is added. The resulting solution is stirred at room temperature for 10 minutes. Then 29.7 g (0.1 mole) of 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5H - dibenzo[a.d]cyclohepten - 5 - one in 25 ml. of dimethyl sulfoxide is added and the mixture is stirred for one hour at room temperature then treated with a three-fold excess of ice-water and extracted with ether. The ether extract is washed with water, dried over anhydrous magnesium sulfate, filtered and evaporated. The residue is distilled at 140°C./0.5 mm. and the distillate is dissolved in ethanol and treated with maleic acid. The precipitate is filtered and recrystallized from diethylether-ethanol 1:1 to give 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene, maleate form m.p. 140—142°C.

EXAMPLE 5:

10 - (2 - Dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene

To a mixture of 5 g of 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene maleate form in 150 ml of methylene chloride there is added 50 ml of 2N - sodium hydroxide, the mixture is shaken, the methylene chloride is dried, filtered and evaporated *in vacuo* to give 10 - (2 - dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene.

WHAT WE CLAIM IS:—

1. 10 - (2 - Dimethylaminoethyl) - 10,11 - dihydro - 2 - fluoro - 5 - methylene - 5H - dibenzo[a,d]cycloheptene.

2. The compound of Claim 1, in acid addition salt form.

3. The compound of Claim 1, in maleate salt form.

4. A pharmaceutical composition comprising the compound of Claim 1, in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutically acceptable diluent or carrier.

B. A. YORKE & CO.,
Chartered Patent Agents,
98, The Centre,
Feltham,
Middlesex, TW13 4EP,
Agents for the applicants.

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